

## APPENDIX B

## Clean Copy of Claims Upon Entry of Preliminary Amendment

1. An isolated specific binding member capable of binding TGF $\beta$ 1, wherein said specific binding member comprises an antigen binding domain comprising a VH CDR3 with an amino acid sequence substantially as set out as the VH CDR3 of SL15 (SEQ ID NO:13) or the VH CDR3 of JT182 (SEQ ID NO:15).
2. A specific binding member according to claim 1 which further comprises a VH CDR1 or a VH CDR2 with an amino acid sequence substantially as set out as one or both of the CS37 VH CDR1 (SEQ ID NO:11) and CS37 VH CDR2 (SEQ ID NO:12).
3. (AMENDED) A specific binding member according to claim 1 which comprises a CDR1 sequence substantially as set out as the CS37 VH CDR1 (SEQ ID NO: 11) and CS37 VH CDR2 (SEQ ID NO: 12).
4. The specific binding member of claim 3 wherein said CDR1, CDR2 and CDR3 sequences are carried by a human antibody framework.
5. An isolated specific binding member capable of binding TGF $\beta$ 1, wherein said specific binding member comprises the SL15 VH domain substantially set out in SEQ ID NO:4.
6. An isolated specific binding member capable of binding TGF $\beta$ 1, wherein said specific binding member comprises the JT182 VH domain substantially set out in SEQ ID NO:10.
7. An isolated specific binding member capable of binding TGF $\beta$ 1, wherein said specific binding member comprises the SL15S VL domain substantially set out in SEQ ID NO:8.
8. An isolated specific binding member capable of binding TGF $\beta$ 1, wherein said specific binding member comprises:
  - (i) a VH domain selected from the group of the SL15 VH domain substantially set out in SEQ ID NO:4 and the JT182 VH domain substantially set out in SEQ ID NO:10; and
  - (ii) a VL domain selected from the group of the SL15S VL domain substantially set out in SEQ ID NO:8 and the SL15A VL domain substantially set out in SEQ ID NO:6.
9. The isolated specific binding member of claim 8 wherein the VH domain is the SL15 VH domain substantially set out in SEQ ID NO:4.
10. (AMENDED) The isolated specific binding member of claim 1 in the form of a single chain Fv (scFv).
11. (AMENDED) The isolated specific binding member of claim 11 in the form of an IgG.

12. The isolated specific binding member of claim 11 wherein said IgG is an IgG1 or IgG4.

13. (AMENDED) A pharmaceutical composition comprising the specific binding member of claim 1 in association with a pharmaceutically acceptable excipient, carrier, buffer or stabiliser.

14. A specific binding member of any one of claims 1 to 12, or a composition of claim 13, for use in a method of treatment of the human or animal.

15. A specific binding member or composition for use according to claim 14 wherein said treatment is to treat a condition associated with extracellular matrix deposition in a patient including glomerulonephritis, keloid and hypertrophic scarring, proliferative vitreoretinopathy, glaucoma drainage surgery, corneal injury and cataracts.

16. A specific binding member or composition for use according to claim 14 in a method of modulating the immune or inflammatory response.

17. A specific binding member or composition for use according to claim 14 in a method of treatment of a tumour.

18. A specific binding member or composition for use according to claim 17 wherein said tumour is associated with angiogenesis or metastasis.

19. A specific binding member or composition for use according to claim 17 or 18 wherein said tumour is a breast, prostate, ovarian, stomach, colorectal, skin, lung, cervical and bladder tumour, or a leukemia or sarcoma.

20. A specific binding member or composition for use according to claim 14 in a method of treating asthma.

21. (AMENDED) A method of treating a condition in a patient, the condition being associated with expression of TGF $\beta$ <sub>1</sub>, which comprises administering to said patient a specific binding member of claim 1.

22. A method according to claim 21, wherein said condition is associated with extracellular matrix deposition in a patient including glomerulonephritis, keloid and hypertrophic scarring, proliferative vitreoretinopathy, glaucoma drainage surgery, corneal injury and cataracts; a tumour including a tumour is associated with angiogenesis or metastasis and/or a tumour selected from the group of breast, prostate, ovarian, stomach, colorectal, skin, lung, cervical and bladder tumours, or leukemias or sarcomas; or asthma.

23. (AMENDED) A method of determining the amount of TGF $\beta$ <sub>1</sub> in a sample which comprises bringing the sample into contact with a specific binding member according to any one of claims 1 to 12, and determining the amount of binding of the specific binding member to TGF $\beta$ <sub>1</sub> in the sample.

24. (AMENDED) An isolated nucleic acid comprising a sequence which encodes the specific binding member of claim 1.

25. An method of preparing a specific binding member capable of binding TGFβ<sub>1</sub>, said method comprising expressing the nucleic acid of claim 24 in a host cell under conditions to provide for expression of said nucleic acid, followed by recovery of said specific binding member.

26. (NEW) A method for obtaining an antibody antigen binding domain specific for TGFβ<sub>1</sub>, the method comprising

providing by way of addition, deletion, substitution or insertion of one or more amino acids in the amino acid sequence of VH domain selected from SEQ ID NO. 4 and SEQ ID NO. 10 a VH domain which is an amino acid sequence variant of the VH domain, and combining the VH domain thus provided with one or more VL domains to provide one or more VH/VL combinations; and/or

providing by way of addition, deletion, substitution or insertion of one or more amino acids in the amino acid sequence of a VL domain selected from SEQ ID NO. 6 and SEQ ID NO. 8 a VL domain which is an amino acid sequence variant of the VL domain, and combining the VL domain thus provided with one or more VH domains to provide one or more VH/VL combinations; and

testing the VH/VL combination or combinations to identify an antibody antigen binding domain specific for TGFβ<sub>1</sub>.

27. (NEW) A method of preparing a specific binding member specific for TGFβ<sub>1</sub>, which method comprises:

providing a starting repertoire of nucleic acids encoding a VH domain which either include a CDR3 to be replaced or lack a CDR3 encoding region;

combining said repertoire with a donor nucleic acid encoding an amino acid sequence substantially as set out herein for SL15 or JT182 VH CDR3 such that said donor nucleic acid is inserted into the CDR3 region in the repertoire, so as to provide a product repertoire of nucleic acids encoding a VH domain; and/or

providing a starting repertoire of nucleic acids encoding a VL domain which either include a CDR3 to be replaced or lack a CDR3 encoding region;

combining said repertoire with a donor nucleic acid encoding an amino acid sequence substantially as set out herein for SL15 or JT182 VL CDR3 such that said donor nucleic acid is inserted into the CDR3 region in the repertoire, so as to provide a product repertoire of nucleic acids encoding a VL domain; and

expressing the nucleic acids of said product repertoire;

selecting a specific binding member specific for TGFβ<sub>1</sub>; and

recovering said specific binding member or nucleic acid encoding it.

28. (NEW) A method of treating a condition in a patient, the condition being associated with expression of TGFβ<sub>1</sub>, which comprises administering to said patient a specific binding member of claim 5.

29. (NEW) A method of treating a condition in a patient, the condition being associated with expression of  $TGF\beta_1$ , which comprises administering to said patient a specific binding member of claim 6.

30. (NEW) A method of treating a condition in a patient, the condition being associated with expression of  $TGF\beta_1$ , which comprises administering to said patient a specific binding member of claim 7.

31. (NEW) A method of treating a condition in a patient, the condition being associated with expression of  $TGF\beta_1$ , which comprises administering to said patient a specific binding member of claim 8.

32. (NEW) A method of treating a condition in a patient, the condition being associated with expression of  $TGF\beta_1$ , which comprises administering to said patient specific binding member of claim 9.

33. (NEW) An isolated nucleic acid comprising a sequence which encodes the specific binding member of claim 5.

34. (NEW) An isolated nucleic acid comprising a sequence which encodes the specific binding member of claim 6.

35. (NEW) An isolated nucleic acid comprising a sequence which encodes the specific binding member of claim 7.

36. (NEW) An isolated nucleic acid comprising a sequence which encodes the specific binding member of claim 8.

37. (NEW) An isolated nucleic acid comprising a sequence which encodes the specific binding member of claim 9.